REVIEW

Randomized Trials for Endovascular Treatment of Infrainguinal Arterial Disease: Systematic Review and Meta-analysis (Part 2: Below the Knee)

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WHAT THIS PAPER ADDS

Endovascular treatment of patients with critical limb ischemia should preferably be done using balloon angioplasty with optional bailout stenting for below-the-knee arterial lesions. The use of drug-eluting balloons in these patients, especially diabetic patients, seems promising, but more studies focusing on clinical outcomes are needed before this strategy can be implemented into standard clinical care. Bare stents, when bailout stenting is indicated, are recommended over drug-eluting stents, as trials have not shown clinically significant differences.

Objective: To evaluate 1 to 48 month follow-up outcomes of different endovascular treatment strategies in below-the-knee (BTK) arterial segments in critical limb ischemia (CLI) patients.

Methods: Medline and Embase were searched (last searched on 5 November 2013) for studies of randomized controlled trials comparing either balloon angioplasty (PTA) or drug-eluting balloon (DEB) with optional bailout stenting, or primary stenting using a bare stent (BS) or drug-eluting stent (DES) to one another. Methodological quality of each trial was assessed using a Cochrane Collaboration's tool, and quality of evidence was assessed using the GRADE system. Outcomes assessed were wound healing, quality of life, change in Rutherford classification, amputation, death, target lesion revascularization (TLR), bypass, binary restenosis, late lumen loss, stenosis grade, and event-free survival with follow-up periods of at least 1 month.

Results: Twelve trials including 1145 patients were identified, with 90% of patients having CLI. Six BS versus PTA and two DES versus PTA trials showed low-quality evidence of equal efficacy. One trial, comparing DEB with PTA, showed moderate-quality evidence of improved wound healing (RR 1.28; 95% CI: 1.05 to 1.56; $p = .01$), improvement in Rutherford classification (RR 1.32; 95% CI: 1.08 to 1.60; $p = .008$), and lower TLR (RR 0.41; 95% CI 0.23 to 0.74; $p = .002$) and binary restenosis (RR 0.36; 95% CI 0.24 to 0.54; $p < .0001$) in diabetic patients after 12 months. Amputation and death rate did not differ significantly. For DES versus BS, most trials showed equal efficacy between strategies.

Conclusion: Based on low- to moderate-quality evidence, PTA with optional bailout stenting using BS should remain the preferred strategy in treating CLI patients with BTK arterial lesions. Before other strategies can be implemented, larger and high-quality RCTs assessing clinically relevant outcomes are needed.

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INTRODUCTION

In 85% of patients with critical limb ischemia (CLI), arterial lesions are located at the above-the-knee or below-the-knee (BTK) arterial segments.[1] In over 50%, the arterial stenosis or occlusion is specifically located at the popliteal or tibial level.[1] As a result of these arterial lesions, tissue perfusion is decreased, clinically resulting into rest pain, or when an ulcer is present, impaired ulcer healing with possible secondary infection and gangrene.[2] The prognosis for patients with CLI is poor, as 1 year after initial presentation, 30% of patients will have had an amputation and 25% will have died.[2]

The aim of treatment for CLI is to prevent amputation by restoring ulcer healing potential, and to prevent death. To enable ulcer healing, revascularization of the limb is essential, either by endovascular or surgical intervention. According to the 2007 Trans-Atlantic Inter-Society Consensus II (TASC II) guideline,[2] there is increasing evidence to support BTK endovascular treatment in patients with CLI and with medical co-morbidity. Infrapopliteal balloon angioplasty (PTA) and stenting is not advised for patients with intermittent claudication.[2]

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In the past decade, several strategies for BTK endovascular intervention have been evaluated, such as PTA versus drug-eluting balloon (DEB) angioplasty with optional bailout stenting, or PTA versus primary stenting using a bare stent (BS) or drug-eluting stent (DES). The idea behind DEBs and DESs is that by delivering drugs such as paclitaxel or sirolimus, neointima formation will be inhibited and the occurrence of restenosis reduced.[3,4] Thereby, tissue perfusion may be improved for a longer period, increasing the potential for ulcer healing. However, conclusive evidence on this is still lacking.

We performed a systematic review to determine overall 1 to 48 month outcomes of RCTs comparing different endovascular treatment strategies in BTK arterial segments in patients with CLI, to select the best endovascular treatment strategy in these patients.

MATERIALS AND METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.[5] The protocol for this review was not published or registered in advance. This review was conducted together with a review on above-the-knee endovascular interventions. We refer to that paper for a detailed description of the materials and methods.[6]

Eligibility criteria

Types of studies. RCTs.
Types of patients. Patients with CLI treated for BTK arterial stenosis or occlusion.
Types of intervention. Studies comparing (1) BS versus PTA, (2) DES versus PTA, (3) DEB versus PTA, or (4) DES versus BS.
Types of outcome measures. Wound healing, quality of life, change in Rutherford classification, amputation, death, target lesion revascularization (TLR), bypasses performed, binary restenosis (patency), late lumen loss, stenosis grade, and event-free survival (EFS) for follow-up periods of at least 1 month.

Information sources

Electronic databases, Medline (PubMed) and OVID Embase, were searched from 1980 to the present. The last search was performed on 5 November 2013.

Search strategy

A detailed search strategy is provided in Appendix 1 (online supplementary material).

Study selection

Two authors (SJ and AC) independently assessed eligibility first by screening titles and abstracts of the identified articles, after which both authors assessed full texts of the remaining eligible articles.

Methodological quality and risk of bias in individual studies

For assessing methodological quality the Cochrane Collaboration's tool for assessing risk of bias was used.[7] Additionally, the presence of baseline differences between the intervention and the comparator strategies for several risk factors in peripheral arterial disease were scored.

Data extraction

Two authors (SJ and AC) independently extracted the data from the included articles, after which consensus was reached. For all outcomes extracted, when separate data were available for patients with CLI, these data were preferred.

Summary estimates of outcomes

Overview of summary estimates. Multiple outcomes were of interest for this review. For dichotomous outcomes such as wound healing, change in Rutherford classification (when dichotomized), amputation, and death, the risk ratio (RR) was the principle summary measure. For continuous outcomes, the summary measure was the weighted mean difference (MD).

Pooling of summary estimates

Data were pooled using the random effects model. Heterogeneity was not tested statistically, but assumed a priori, because of differences in population and lesion characteristics and the use of different types of stents or balloons between studies.

Quality of evidence

For every outcome the quality of evidence was assessed in consensus by two authors (SJ and AC) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[8] For this review, because of the inability to assess inconsistency and publication bias for most outcomes, quality of evidence was downgraded to moderate quality in advance for all outcomes. Risk of bias was defined as present, when five or more items on the Cochrane Collaboration's tool were graded as unclear or high risk of bias. Imprecision was defined as present when less than 100 patients were evaluated for an outcome.

Summary of findings per comparison

Finally, the quality of evidence and the results of each trial were combined in one value to give an overview of the findings. When outcomes between strategies were significantly different ($p < .05$) in favor of the intervention strategy the outcomes were scored as $+$, $++$, or $+++$, depending on the corresponding quality of evidence. When a significant difference was in favor of the comparator strategy, the outcomes were scored as -, - -, or - - -, depending on the corresponding quality of evidence. When outcomes between strategies were not significantly different ($p \geq .05$) the outcomes were scored as $=$, $==$, or $===$, depending on the corresponding quality of evidence. When conflicting evidence was present, and data

could not be pooled, both qualities of evidence would be depicted in the summary of findings table.

RESULTS

Study selection

The search yielded 3658 articles, 2758 in Medline and 900 in Embase. Removal of 427 duplicates led to 3231 articles to be assessed for eligibility based on title and abstract. This resulted in exclusion of 3167 articles. For 64 articles, full-text had to be assessed before deciding whether they were eligible for this systematic review. Fifty-one articles were excluded, as 29 were RCTs of above-the-knee intervention, 21 were only abstracts for conference meetings, and one was a protocol publication. Finally, 13 articles[9–21] were included in this review. Fig. 1 is a flow diagram of the selection process.

Study characteristics

Patients. The 13 included articles were publications of 12 RCTs of 1145 patients in total. In these trials, six (6 publications,[9–14] 379 patients) compared BS with PTA, two (2 publications,[14,15] 228 patients) DES with PTA, two (2 publications,[16,17] 182 patients) DEB with PTA, and four (5 publications,[14,18–21] 381 patients) DES with stent. Eight trials included only patients with CLI, and, overall, for all studies reporting prevalence of IC and CLI, patients had CLI in 90% of patients. For all trials, the mean age ranged between 67 and 76 years, 65% of the patients were male, 67% had diabetes, and 30% were smokers. The mean lesion length for RCTs ranged between 11 and 130 mm (median 30 mm). Full study characteristics are shown in Table 1.

Comparisons. One trial[14] compared four strategies directly: PTA, PTA with intravenous (iv.) abciximab administration, BS with iv. abciximab administration and DES with iv. abciximab administration. As the effect of abciximab was not of interest for this review, the groups compared were the ones with abciximab administration. The two trials[14,15] comparing DES with PTA, and three[14,18–20] of the four trials comparing DES with BS, used sirolimus-eluting stents. The other trial[21] comparing DES versus BS used an everolimus-eluting stent. All trials on DEB used paclitaxel-coated balloons.[16,17] One[16] of these trials studied DEB in both above-the-knee and BTK arterial lesions.

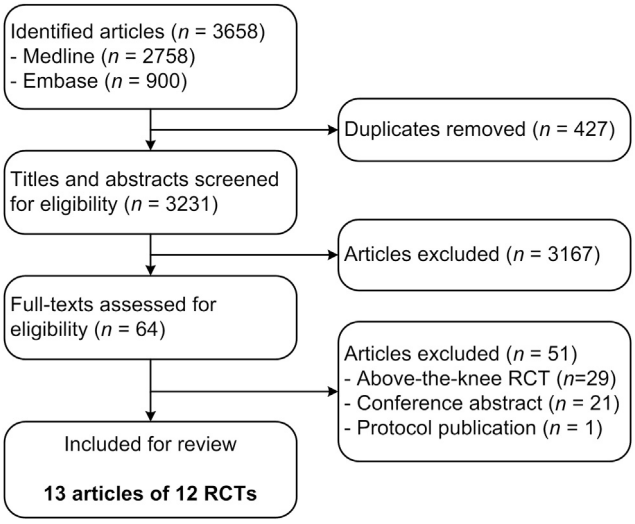

Figure 1. Flow diagram of search and study selection. RCT, randomized controlled trial.

Outcomes. Follow-up of patients varied from 1 to 48 months. The primary end point reported for most trials was 6-month or 1-year primary patency, binary restenosis, or late lumen loss. One trial[9] comparing BS with PTA, reported 1-year Rutherford classification change, and one trial[11] reported 3- and 9-month clinical improvement, that is based on the American Heart Association Clinical Improvement Score, and limb salvage as primary end point.

Methodological quality and risk of bias

For all trials, allocation concealment and sequence generation were performed adequately or were not sufficiently reported, resulting in an unclear risk of bias. One trial[17] (8%) had a low risk of bias for baseline characteristics, whereas five trials[9,11–14] (42%) had differences in baseline characteristics, and were therefore subject to a high risk of bias. Blinding during intervention was not possible for trials comparing BS or DES with PTA, resulting in 11 trials[9–17,20,21] (92%) with a high risk of bias. One trial[18,19] was able to blind the use of DES versus BS during intervention. For item blinding during outcome assessment, incomplete outcome data, and selective outcome reporting, the majority of trials had a low or unclear risk of bias. Two trials[16,17] (17%) had a low risk for other biases, whereas the other trials (83%) had a high risk of bias because of high loss to follow-up rate or the ability for selective additional treatments.

Methodological quality per trial is shown in Fig. 2, and overall methodological quality of trials per risk of bias item is shown in Fig. 3.

Summary of findings per comparison

The summary of findings for each outcome is depicted in Table 2. The outcomes extracted from every trial are shown in Appendix 2 (online supplementary material). An overview of the quality of evidence per outcome is shown in Appendix 3 (online supplementary material). The summary findings per comparison are described below.

BS versus PTA. Trials on wound healing, change in Rutherford classification, and amputation rate had mainly a low- or very low-quality of evidence. Overall, most outcomes were equal for the BS and PTA strategy between 1 and 48 months follow-up. Six-month restenosis showed conflicting evidence for the BS strategy compared with PTA. A meta-analysis of two trials[13,14] showed significantly less restenosis in the PTA group (RR 1.69, 95% CI: 1.17 to 2.44, $p = .005$), whereas one trial[10] performed Kaplan–Meier survival analysis, and reported that 79.7% of patients in the BS group and 45.6% in the PTA group were free from binary restenosis, with a statistically significant difference ($p = .0235$). One other trial performing the same analysis

Table 1. Study and patient characteristics.

First author	Comparison	Patients, *N*	% FII/FIII/FIV or IC/CLI	Lesions, *N*	Age (y), mean (SD) or median (range)	Males, *N* (%)	Smoking, *N* (%)	Diabetes, *N* (%)	Renal failure, *N* (%)	CAD, *N* (%)	Stroke, *N* (%)	Hyperlipidemia, *N* (%)	Hypertension, *N* (%)	Occlusions, *N* (%)	Stenosis in %, mean (SD)	Lesion length (mm), mean (SD)	Primary outcome	Industry sponsored
BS vs PTA																		
Brodmann 2011[9]	Carbon-S	54	0/39/61	54	73 (2)	26 (48)	15 (28)	40 (74)	—	47 (87)	47 (87)	20 (37)	46 (85)	16 (30)	—	—	1 y RF improvement	No
Rand 2006[10]	Carbon-S	51	0/24/76	95	Mean 72 (47—80)	—	31 (61)	35 (69)	8 (16)	20 (39)	—	50 (98)	—	7 (7)	—	24 (5—30)	6 mo patency rate	No
Rand 2011[11]	Carbon-S	89	0/12/88	131	72 (9)	58 (65)	—	69 (78)	—	—	—	—	—	31 (24)	69 (21)	—	3 and 9 mo clinical improvement and limb salvage	Yes
Randon 2010[12]	Variety of S	38	0/13/87	56	72 (10)	20 (53)	5 (13)	22 (58)	10 (26)	30 (79)	5 (13)	16 (42)	38 (100)	36 (64)	—	—	1 y freedom from amputation and primary patency	No
Bosiers 2009[13]	AMS	117	0/27/73	149	74 (8)	72 (62)	50 (43)	82 (70)	—	—	—	67 (57)	102 (87)	—	—	11 (5)	30 d safety (major amp/death) and 6 mo patency	Yes
Tepe 2010[14]	BMS abciximab vs POBA abciximab	30	0/0/100	30	75 (—)	18 (60)	2 (7)	22 (73)	—	—	—	13 (43)	21 (70)	10 (33)	89 (—)	33 (17)	6 mo primary restenosis	Not reported
DES vs PTA																		
Scheinert 2012[15]	Sirol-ES	200	FII—FIV	228	73 (9)	143 (72)	65 (33)	129 (65)	—	90 (45)	—	146 (73)	181 (91)	179 (79)	—	27 (21)	12 mo binary restenosis	Yes
Tepe 2010[14]	Sirol-ES abciximab vs POBA abciximab	28	0/0/100	28	71 (—)	16 (57)	4 (14)	21 (75)	—	—	—	12 (43)	22 (79)	8 (29)	90 (—)	29 (21)	6 mo primary restenosis	Not reported
DEB vs PTA																		
Fanelli 2012[16]	PTX-EB	—	FII—FIV	30	—	—	—	—	—	—	—	—	—	12 (40)	86 (5)	—	6 mo LLL	No
Liistro 2013[17]	PTX-EB	132 (143 limbs)	FIII—FIV	158	75 (10)	106 (80)	20 (15)	132 (100)	—	22 (17)	12 (9)	39 (30)	98 (74)	126 (80)	97 (8)	130 (81)	12 mo binary restenosis	No
DES vs BS																		
Rastan 2011[19]/ 2012[18]	Sirol-ES vs BMS	161	53/47	161	73 (9)	107 (66)	46 (29)	87 (54)	57 (35)	—	—	123 (76)	145 (90)	36 (22)	88 (9)	31 (9)	1 y primary patency rate	Yes
Falkowski 2009[20]	Sirol-ES vs BMS	50	68/20/12	50	mean 69 (53—58)	29 (58)	22 (44)	20 (40)	—	21 (42)	7 (14)	18 (36)	31 (62)	—	—	18 (3)	6 mo restenosis	Not reported
Tepe 2010[14]	Sirol-ES abciximab vs BMS abciximab	30	0/0/100	30	73 (—)	16 (53)	2 (7)	15 (50)	—	—	—	9 (30)	21 (70)	10 (33)	89 (—)	31 (21)	6 mo primary restenosis	Not reported
Bosiers 2012[21]	Everol-ES vs BMS	140	0/45/55	154	76 (8)	89 (64)	45 (32)	77 (55)	44 (31)	—	—	53 (38)	96 (69)	25 (14)	—	17 (10)	1 y primary patency	Yes

AMS = absorbable metal stent; BMS = bare metal stent; BS = bare stent; CAD = coronary artery disease; d = days; DEB = drug-eluting balloon; DES = drug-eluting stent; EB = eluting balloon; ES = eluting stent; Everol = everolimus; FII/FIII/FIV = Fontaine stage II, III, or IV; LLL = late lumen loss; mo = month; *N* = number; PTA = plain old balloon angioplasty; PTX = paclitaxel; RF = Rutherford; S = stent; SD = standard deviation; Sirol = sirolimus; y = years.

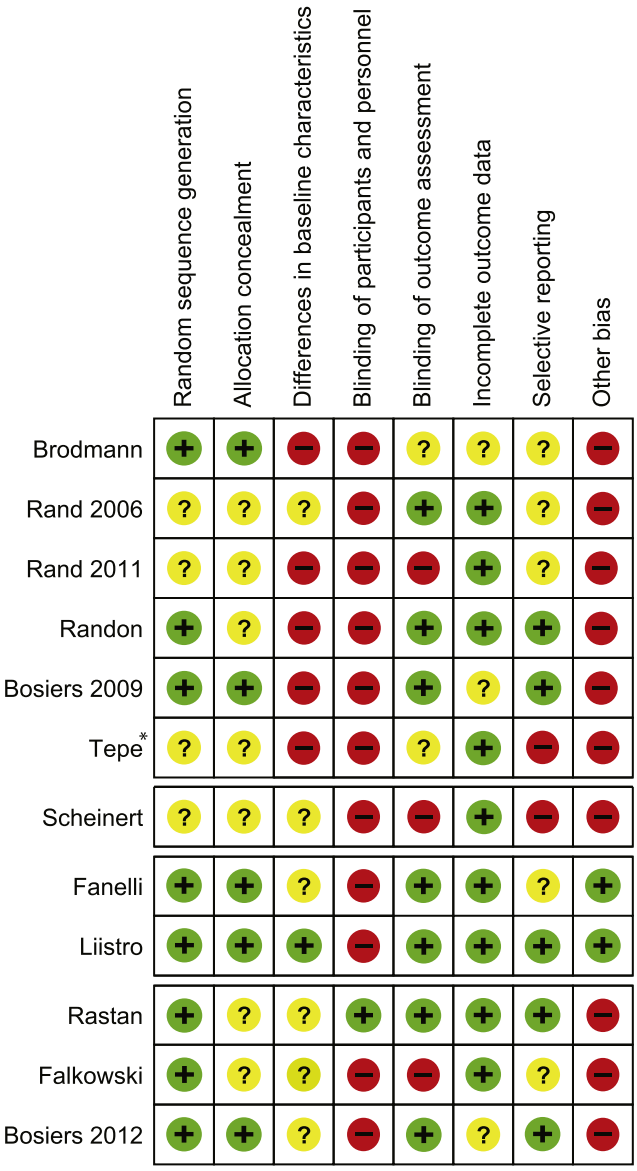

Figure 2. Methodological quality and risk of bias per individual RCT. The items were scored as adequate (+), unclear (?), or inadequate (-). The figure is divided into four parts, from top to bottom, respectively, BS versus PTA, DES versus PTA, DEB versus PTA, and DES versus BS. * The study of Tepe et al. compared multiple strategies, that is BS versus PTA, DES versus PTA, and DES versus BS.

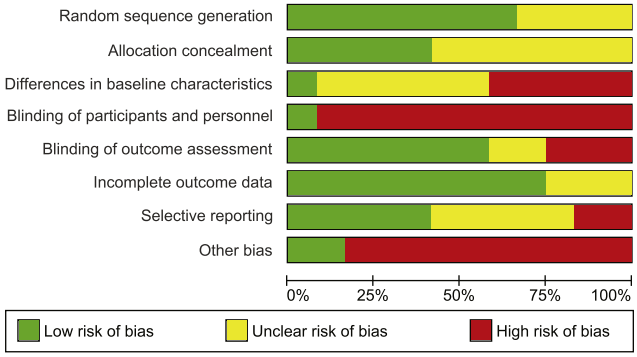

Figure 3. Methodological quality per item.

reported no statistically significant difference on the 6-month binary restenosis between groups. Fig. 4 shows a meta-analyses and forest plots of 6-month TLR and binary restenosis.

DES versus PTA. The quality of evidence was mainly very low for the comparison DES versus PTA. Most outcomes, that is wound healing, change in Rutherford classification, amputation, death, and TLR, were equal for the DES and PTA strategy between 2 and 48 months follow-up. DES had a beneficial effect on binary restenosis and stenosis grade compared with PTA at 12-month follow-up.

DEB versus PTA. For the comparison of DEB versus PTA, 12-month follow-up was available in diabetic patients. For the outcomes wound healing (RR 1.28; 95% CI: 1.05 to 1.56; $p = .01$), change in Rutherford classification (RR for Rutherford improvement 1.32; 95% CI: 1.08 to 1.60; $p = .008$), TLR (RR 0.41; 95% CI: 0.23 to 0.74; $p = .002$) and binary restenosis (RR 0.36; 95% CI: 0.24 to 0.54; $p < .0001$), moderate evidence in one trial[17] showed a higher efficacy with the use of DEBs. The outcomes amputation and death rate did not differ significantly between strategies.

DES versus BS. Very low-quality evidence showed equal wound healing rates between DES and BS. Some trials showed a better efficacy of DES for the outcome change in Rutherford classification, whereas other trials showed equal efficacy at 12-month follow-up. Most trials showed very low- to moderate-quality evidence for equal efficacy between strategies. For binary restenosis, late lumen loss, and stenosis grade, low- to moderate-quality of evidence showed a better efficacy for the use of DES after 12-month follow-up. Fig. 5 is a meta-analysis and forest plot of 12-month binary restenosis.

DISCUSSION

Summary of evidence

One trial[17] comparing the use of paclitaxel-DEB with PTA, showed moderate evidence of significantly better wound healing and Rutherford improvement, and lower TLR rate and binary restenosis after 12-month follow-up with the DEB strategy in diabetic patients. There is low to moderate evidence showing that a primary stenting strategy using either BS or sirolimus-DES does not perform better than PTA with optional bailout strategy. Sirolimus- or everolimus-DES clinically performed equally compared with BS, but performed better in terms of binary restenosis and late lumen loss.

Implications for practice

PTA with optional bailout stenting for BTK arterial lesions in patients with CLI is still the preferred strategy. The use of DEBs in these patients, especially diabetic patients, may be beneficial, but high-quality and adequately powered trials focusing on clinical outcomes are needed before this strategy can be implemented into standard clinical care. The use of BS when bailout stenting is indicated is recommended, as DES trials did not show clinical benefit from DES over BS.

Table 2. Summary of findings per comparison.

BS vs PTA	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	24 mo	24–48 mo
Wound healing		=		=		–		=
Quality of life								
RF change			=	= =		=		
Minor amputation		=	=	=	=		= =	=
Major amputation	= = =	=	=	= = =	=	= =	= =	=
Total amputation		=	=	=	=		= =	=
Death	= = =		=	= = =	=	= =	= =	=
TLR		=	=	= = (MA)	=			
Bypass				=			= =	
Binary restenosis		=		- - (MA)/+/= = =	=	= =		
Late lumen loss				–				
Stenosis grade					=			
EFS								

DES vs PTA	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	24 mo	24–48 mo
Wound healing		-		=				=
Quality of life								
RF change		= =		= =				
Minor amputation		=		=				=
Major amputation		=		=				=
Total amputation		=		=		= =		=
Death						= =		=
TLR		=				= =		
Bypass								
Binary restenosis		+		=		++		
Late lumen loss						= =		
Stenosis grade						++		
EFS								

DEB vs PTA	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	24 mo	24–48 mo
Wound healing						+++		
Quality of life								
RF change						+++		
Minor amputation						= = =		
Major amputation						= = =		
Total amputation						= = =		
Death						= = =		
TLR						+++		
Bypass								
Binary restenosis						+++		
Late lumen loss				++				
Stenosis grade								
EFS								

DES vs BS	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	24 mo	24–48 mo
Wound healing		=		=				=
Quality of life								
RF change				= = =		= =		++
Minor amputation		=		=		= =		= =
Major amputation		=		=		= =		= =
Total amputation		=		=		= =		= =
Death				= = =		= = =		= =
TLR		=		+		+++/= =		
Bypass								
Binary restenosis		=		++ (MA)		+++ (MA)		
Late lumen loss				+		++		
Stenosis grade						++		
EFS								= =

+, ++, or +++ refers to, respectively, very low-, low-, or moderate-quality evidence for a significant difference ($p < .05$) in favor of the intervention strategy. -, - -, or - - - refers to, respectively, very low-, low-, or moderate-quality evidence for a significant difference ($p < .05$) in favor of the comparator strategy (e.g. PTA). =, = =, or = = = refers to, respectively, very low-, low-, or moderate-quality evidence for non-significant difference ($p \geq .05$) between strategies. When conflicting evidence was present in trials, and data could not be pooled, both qualities of evidence were depicted.BS = bare stent; DEB = drug-eluting balloon; DES = drug-eluting stent; mo = month; EFS = event-free survival; MA = meta-analysis; PTA = plain old balloon angioplasty; RF = Rutherford; TLR = target lesion revascularization.

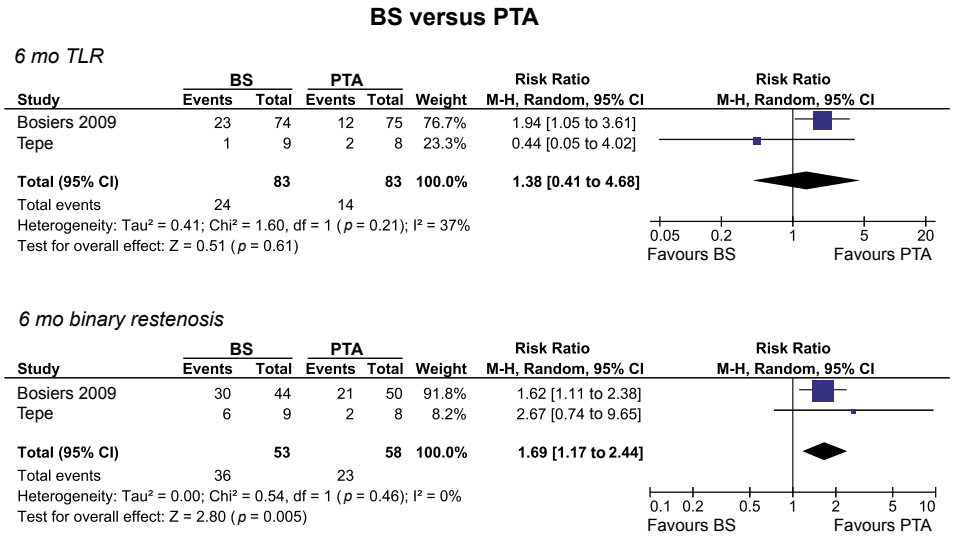

Figure 4. Forest plots of 6-month target lesion revascularization (TLR) and binary restenosis of bare stent (BS) versus plain old balloon angioplasty (PTA).

Limitations of this study

Clinically relevant end points for patients with CLI are wound healing, quality of life, and limb salvage. However, most outcomes reported by the trials included in our review were radiological, such as primary patency, binary restenosis, and late lumen loss. Moreover, only three trials reported on wound healing and not a single trial assessed change in quality of life or functional status using a disease-specific questionnaire. More trials assessing patient reported outcomes are needed before the most clinically relevant endovascular strategy can be selected confidently.

In the meta-analysis we pooled the results of trials with different types of stents, such as balloon- or self-expandable stents, and different drugs for drug-eluting stents, that is sirolimus- and everolimus-eluting stents. Everolimus is a derivative of sirolimus, and a recent RCT on coronary artery stenting showed no significant differences in clinical and angiographic outcomes.[22] However, combining outcomes of different types of stents results in an overall outcome, and cannot identify which type of stent performs best.

The majority of patients with CLI will have multilevel disease.[1] For adequate treatment of such patients, hemodynamic inflow, that is proximal lesions, should be restored before BTK lesions are treated. Several trials reported that, at the judgment of the interventional radiologist, proximal lesions could be treated first. It remains, therefore, questionable whether this could have introduced a selection or performance bias, by for instance treating proximal lesions in patients elected for BTK stenting more extensively.

Four out of twelve trials included patients with intermittent claudication, and in two of these trials such patients were in the majority.[18–20] For patients with intermittent claudication, the clinical outcomes such as wound healing, amputation, and death are not relevant or the event rate is very low. Therefore, by including these patients, the comparison between strategies is more likely to give equal results. This is a major weakness of these trials, and leads to underestimations of potentially significant differences between strategies, and therefore results are not directly applicable to the majority of practice.

The quality of evidence assessment by the GRADE system could not be performed for all domains. The domains heterogeneity and publication bias could not be assessed for one outcome, as the outcomes and follow-up times between studies varied. To compensate for this, quality of evidence was downgraded at forehand with one grade. Therefore, no outcome could have the highest quality of evidence. Moreover, because of the poor scores of many studies on the risk of bias assessment, quality of evidence was low for several outcomes. This low quality of evidence severely affects the strength of recommendation given in this review.

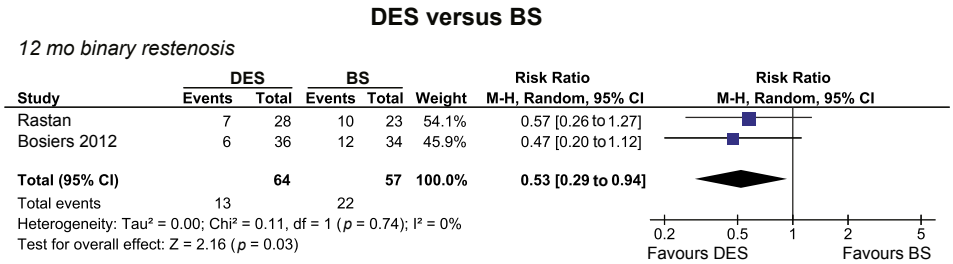

Figure 5. Forest plots of 12-month binary restenosis of drug-eluting stent (DES) versus bare stent (BS).

When PTA gives an inadequate result, bailout stenting is the standard operating procedure.[2] However, several trials considered bailout stenting as a failure for the PTA strategy, resulting in irrelevant data reported for the outcomes binary restenosis and TLR. These data were excluded from this review as bailout stenting is incorporated in the PTA strategy.

Considering the abovementioned limitations, future studies should improve their methodological quality. Furthermore, when comparing two stents, future trials need to shift their focus to comparing bailout DES with bailout BS. Several trials are being performed currently, such as the EXPAND,[23] SENS-BTK[24] (both nitinol stent versus PTA), INPACT-DEEP,[25] Lutonix-BTK[26] (both DEB versus PTA), and the PADI trial[27] (DES versus PTA). Four of these trials still have an angiographic outcome as primary outcome, but sample sizes are larger, ranging between 94 and 480 patients. Three of these trials are industry sponsored, and four trials include only CLI patients. Unpublished results of the INPACT-DEEP trial recently resulted in a safety warning and a recall for all INPACT Amphirion DEBs.[25] The trial showed a trend towards a higher 12-month major amputation rate in the DEB group, without a specific causal relationship after subgroup and multivariate analysis.

We did not find any cost-effectiveness analyses. Yet, these are important as strategies other than PTA, especially using drug-eluting devices, are expensive.[28] For implementing new strategies, evidence for cost-effectiveness of the new strategy must be available.

CONCLUSION

The generally low- to moderate-quality of evidence makes it difficult to draw firm conclusions. Nevertheless, the available evidence indicates that PTA with optional bailout stenting should remain the preferred strategy in treating CLI patients with BTK arterial lesions. Before other strategies can be implemented, larger and high-quality RCTs assessing clinically relevant outcomes are needed.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ejvs.2014.02.012.

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